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10/645,312	08/20/2003	Taeyoung Yoon	58288 (72021)	7622

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EXAMINER

TUCKER, ZACHARY C

ART UNIT PAPER NUMBER

1624

DATE MAILED: 07/06/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

10/645,312

Applicant(s)

YOON ET AL.

Examiner

Zachary C. Tucker

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☐ Responsive to communication(s) filed on ____.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-26 is/are pending in the application.
- 4a) Of the above claim(s) 15-25 is/are withdrawn from consideration.
- 5) ☒ Claim(s) 26 is/are allowed.
- 6) ☒ Claim(s) 1,2 and 4-14 is/are rejected.
- 7) ☒ Claim(s) 3 is/are objected to.
- 8) ☐ Claim(s) ____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☒ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on ____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
 - ☐ Certified copies of the priority documents have been received in Application No. ____.
 - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 15Mar04.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. ____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: ____.

DETAILED ACTION

Election/Restrictions

Restriction to one of the following inventions is required under 35 U.S.C. 121:

- I. Claims 1-14 and 26, drawn to chemical compounds, classified in class/subclasses 544/120, 295, 405 and 408
- II. Claims 15-20, drawn to methods of treating depression, anxiety, "stress," irritable bowel syndrome or Crohn's disease, and pharmaceutical compositions and packages comprising compounds according to Group I as set forth *supra*, classified in classes/subclasses 514235.8, 252.11, 255.05 and 255.06
- III. Claims 21-25, drawn to methods of demonstrating the presence or absence of CRF₁ receptors in a biological sample with a labeled compound according to claim 1, Group I, classified in class/subclass 436/501.

The inventions are distinct, each from the other because:

Inventions I and II or III are distinct, each from the other because they are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case diseases treated by the method according to claim 15, such as depression and anxiety, are treatable by many materially different compounds, such as

Art Unit: 1624

Selective Serotonin Reuptake Inhibitors and GABA agonists, while CRF receptors are detectable by different means than are recited in instant claims 21-25, such as with other CRF receptor ligand compounds. Claim 1 compounds are also not limited in their utility to only CRF receptor antagonists – the rejection under 35 U.S.C. 103(a), based on WO 98/38174 (Cox et al), which follows is based upon a reference teaching compounds according to the instant invention as anticonvulsant compounds.

The method in Group III is not exactly commensurate in scope with Group I, because claim 21 calls for a labeled compound according to claim 1. There is no antecedent basis for a labeled compound in claim 1. The separation and detection steps further differentiate that Group from the methods in Group II, which recite only administering the compound to a patient.

According to the MPEP §803, "...a serious burden on the examiner may be *prima facie* shown if the examiner shows by appropriate explanation of separate classification, or separate status in the art, or a different field of search as defined in MPEP § 808.02. That *prima facie* showing may be rebutted by appropriate showings or evidence by the applicant." Groups I, II and III are separately classified, providing evidence of a search burden.

Because these inventions are distinct for the reasons given above and have acquired a separate status in the art as shown by their different classification and divergent subject matter, restriction for examination purposes as indicated is proper.

During a telephone conversation between the examiner and John B. Alexander on 29 June 2005, provisional election was made with traverse to prosecute the

Art Unit: 1624

invention of Group I, claims 1-14 and 26. Affirmation of this election must be made by applicant in replying to this Office action. Claims 15-25 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to non-elected inventions.

Upon allowance of Group I, the methods, composition and package of Group II will be rejoined and examined for compliance with 35 U.S.C. 101, 112, 102 and 103, and the Requirement for Restriction between Groups I and II, as set forth *supra* will be withdrawn at such time.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 12-14 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 12-14 each specify that the compounds of those claims have a certain K_i value in a "standard in vitro CRF receptor binding assay." There is no such "standard" assay. The K_i value observed will be dependent on the conditions of the assay, as applicants are aware. Since no specific and exact set of conditions are accepted as being the standard CRF binding assay, the K_i values will vary, and therefore the identity of the compounds according to claims 12-14 will vary also. Thus, the scope of claims 12-14 is indefinite.

Art Unit: 1624

Applicants may opine that since there is a standard technique in determining K_i values, then such is a "standard assay." Merely because there is a standard *procedure*, such as measuring the degree to which radiolabelled CRF is displaced from receptors produced by cultured cells, by a certain compound does not mean that a standard concentration, standard CRF receptor (what species of animal), standard pH, standard buffer solution, standard temperature, and standard manner of detecting radiolabelled CRF are accepted by those of ordinary skill. In fact, the specification, where the binding assay is described, states that the procedure employed by applicants was actually a *modified* version of an assay described by Grigoriadis and De Souza (*Methods in Neurosciences*, vol. 5, 1991). So, it is not clear from a reading of the specification exactly what applicants consider the "standard in vitro CRF receptor binding assay" to be.

Claims 12-14 have been examined on the merits as though all compounds embraced by the instant claims have the properties recited in instant claims 12-14, because at page 4, lines 12-15 of the instant specification, this statement appears:

Preferred compounds of Formula I exhibit high affinity for CRF1 receptors, i.e., they bind to, activate, inhibit, or otherwise modulate the activity of receptors other than CRF receptors with affinity constants of less than 1 micromolar, preferably less than 100 nanomolar, and most preferably less than 10 nanomolar.

and at pages 14, lines 1-3 and page 15, lines 13-20, "preferred compounds" are further described chemically as being those wherein "Ar" is phenyl, substituted at the 2, 4, and 6 positions with halogen, alkyl, alkoxy or haloalkoxy. Therefore, those "preferred" compounds possess the properties described at page 4, also, because they

are the preferred compounds, as set out in the specification. All compounds from the Yoon et al reference, cited *infra* in the rejections under 35 U.S.C. 102(a), have such a substitution pattern about the phenyl ring.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

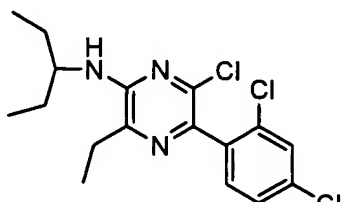
A person shall be entitled to a patent unless –

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1,2,4-9 and 12-14 are rejected under 35 U.S.C. 102(a) as being anticipated by WO 01/60806 (Yoon et al).

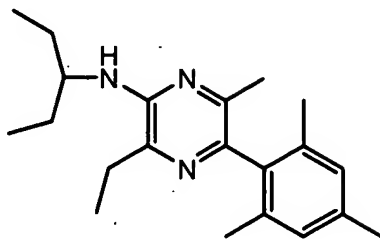
Yoon et al discloses CRF₁ receptor antagonists; many compounds according to the instant claims are disclosed in Yoon et al, which was published less than one year prior to the filing date of the provisional application upon which the instant application is based. There appears to be ample support for the compounds according to the instant claims in said provisional application.

The following compounds are disclosed in Yoon et al, and are shown by molecular structure, along with where those compounds are found in the Yoon et al publication and which of the instant claims they anticipate –



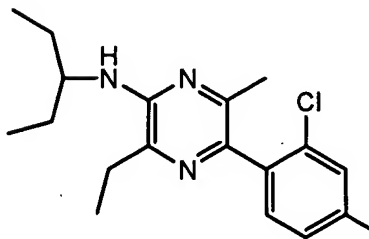
page 83, example 81; anticipates claims 1, 2, 4, 5 and 12-14.

Art Unit: 1624



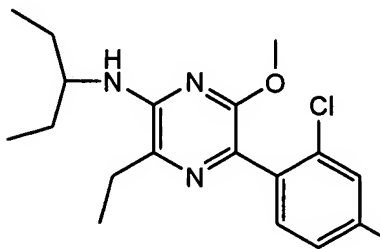
page 49, example 22; anticipates claims 1, 2, 4, 5 and

12-14.



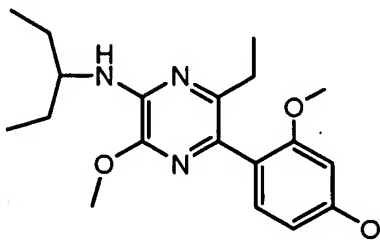
page 84, example 84; anticipates claims 1, 2, 4, 5

and 12-14.



page 87, example 86; anticipates claims 1, 2, 4, 5

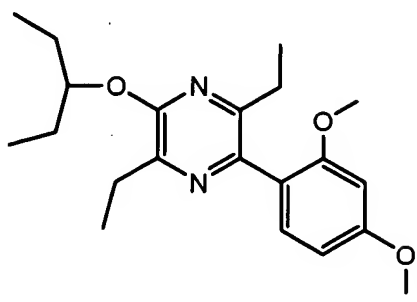
and 12-14.



page 115, example 100; anticipates claims 1, 2, 4, 5,

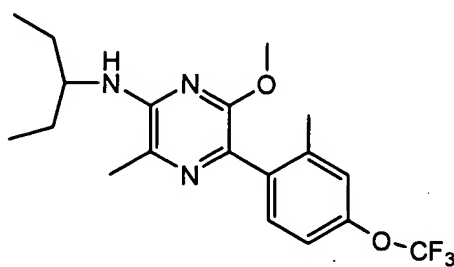
6 and 12-14.

Art Unit: 1624



page 70, example 62; anticipates claims 1, 2, 7, 8,

9 and 12-14.



page 145, example 279; anticipates claims 1, 2,

4, 5 and 12-14.

In all of these compounds R_x is 1-ethylpropyl; R_1 is either ethyl or methoxy; R_3 is methyl, ethyl, chloro or methoxy; J and K are both CH; R_5 is methyl, chloro or methoxy; R_7 is methoxy, methyl or chloro; R_8 is hydrogen or methyl; G is NH or O.

Claims 12-14 are included in this rejection because the specification teaches that ALL of the compounds having substitution on the phenyl ring at 2, 4 and 6 positions with halogen, alkyl, alkoxy or haloalkoxy have the preferred receptor binding properties set out in claims 12-14, namely that the receptor binding constant, K_i , of those compounds is less than 10nM. An explanation of this rationale is found in the section headed "Claim Rejections - 35 USC § 112," where claims 12-14 are rejected for indefiniteness.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

Art Unit: 1624

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/60806 (Yoon et al).

Yoon et al is applied to claim 10 as set forth above in the rejection of claims 1,2,4-9 and 12-14 under 35 U.S.C. 102(a).

At the time the invention was made, compounds according to claim 10 would have been obvious to one of ordinary skill in the art given the teaching of Yoon et al.

The compound depicted above in the rejections under 35 U.S.C. 102(a), which has -O- at the "G" position would have been obvious to modify whereby the R₁ group, which is ethyl in that compound, were replaced with methylamino. -NH(C₁₋₄alkyl) is expressly suggested at R₁ as one of the preferred embodiments at lines 24-26. Methylamino would be at once envisaged by one of ordinary skill given the suggestion of "-NH(C₁₋₄alkyl)."

The deficiency of Yoon et al with respect to claim 10 is that no specific compound according to claim 10 is exemplified in that publication.

When considering the general teachings in a disclosure of an invention, one of ordinary skill in that art necessarily must look to the exemplified embodiments in order to determine how the general teachings apply to the invention. In the case of Yoon et al, one of ordinary skill would look to the exemplified compounds. The suggestion to put methylamino at R₁ is clear. Therefore, substitution of a methylamino group at R₁ of any of the exemplified compounds is obvious in light of the teachings of Yoon et al. The

Art Unit: 1624

motivation to do so would have been to make CRF receptor antagonists for the treatment of anxiety and depression. There would have been a high expectation of success, as this modification is suggested by Yoon et al to make CRF receptor antagonists.

Claim 11 is rejected under 35 U.S.C. 103(a) as being unpatentable over WO 01/60806 (Yoon et al).

Yoon et al is applied to claim 11 as set forth above in the rejection of claims 1,2,4-9 and 12-14 under 35 U.S.C. 102(a).

At the time the invention was made, compounds according to claim 10 would have been obvious to one of ordinary skill in the art given the teaching of Yoon et al.

The deficiency of Yoon et al with respect to claim 11 is that no specific compound according to claim 11 is exemplified in that publication.

The last depicted compound above in the rejections under 35 U.S.C. 102(a) is, save for the methyl group at the R₁ position, the same as the species N-(1-ethylpropyl)-3,6-dimethoxy-5-[2-methoxy-4-(trifluoromethoxy)phenyl]pyrazin-2-amine, named in instant claim 11 at page 16 of the correspondence in which the preliminary amendment filed 7 January 2005 is found. The species referred to in instant claim 11 would have been obvious in light of the general teachings found in Yoon et al, considered in light of what compounds are exemplified in that publication.

When considering the general teachings in a disclosure of an invention, one of ordinary skill in that art necessarily must look to the exemplified embodiments in order to determine how the general teachings apply to the invention. In the case of Yoon et

Art Unit: 1624

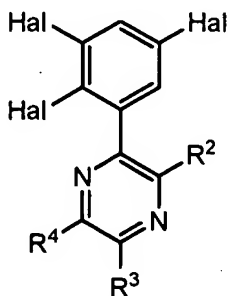
al, one of ordinary skill would look to the exemplified compounds. The suggestion to put methoxy at R₁ is clear. Therefore, substitution of a methoxy group at R₁ of any of the exemplified compounds, including the compound of example 279 where R₁ is methyl, is obvious in light of the teachings of Yoon et al. The motivation to do so would have been to make CRF receptor antagonists for the treatment of anxiety and depression. There would have been a high expectation of success, as this modification is suggested in the Yoon et al publication.

In fact, many of the exemplified compounds DO have a methoxy group at R₁, so this modification of the compound of Yoon et al's example 279 is especially obvious.

Claims 1 and 2 are rejected under 35 U.S.C. 103(a) as being unpatentable over WO 98/38174 (Cox et al).

At the time the invention was made, compounds according to instant claims 1 and 2 would have been obvious to one of ordinary skill in the art, given the teaching of Cox et al.

Cox et al teaches anticonvulsant compounds for the treatment of epilepsy, preferably having the structure of "formula (Ib)," found on page 6 of the publication, which is as follows



Art Unit: 1624

In these compounds, "Hal," of course is halogen, preferably chloro-; R^2 is $-NH_2$ or $NHC(=O)R^a$; R^3 is $-NR^bR^c$ or $-NHC(=O)R^a$ or hydrogen; R^4 is hydrogen, C_{1-4} alkyl (preferably methyl), C_{1-4} alkyl (preferably methyl) substituted by one or more halogen atoms, $-CN$, $-CH_2OH$, $-CH_2OR^d$ or $-CH_2S(O)_xR^d$.

These variables are all defined on page 5 of Cox et al.

The deficiency of Cox et al with respect to instant claims 1 and 2 is that no specific compound of claims 1 and 2 was made by Cox et al and reported in that publication.

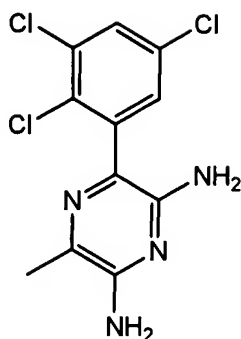
Compounds according to instant claims 1 and 2 are expressly suggested in the reference, however.

One of ordinary skill understands the general teachings in a publication disclosing an invention wherein the invention is a family of chemical compounds to be particularly applicable to those embodiments of the invention which are exemplified.

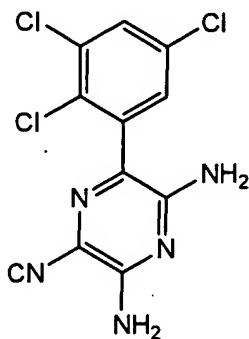
Cox et al exemplifies several compounds, and these are named on page 6, lines 9-26. Particularly relevant are the following compounds. Structures are provided as well:

5-methyl-2,6-diamino-3-(2,3,5-trichlorophenyl)pyrazine, which has this structure:

Art Unit: 1624



and 5-cyano-2,6-diamino-3-(2,3,5-trichlorophenyl)pyrazine, which has this structure:



These two compounds correspond to the structure in instant claim 1 wherein G is NH, R₁ is either methyl or cyano, R₃ is amino, R₅ is chloro, K is CR₆ and R₆ is halogen, J is CH (R₉ is hydrogen) and R_x is hydrogen. Instant claim 1 does not permit hydrogen, however, and that is why this rejection is set forth under 35 U.S.C. 103(a), not 102(b).

Cox et al expressly suggests that at his R³ position, which corresponds to -G-R_x in the instantly claimed compounds, that the amino group at that position is substituted with R^b and R^c (page 4, lines 27 and 28). R^b and R^c are hydrogen or C₁₋₄ alkyl.

So, one of ordinary skill in the art would find it obvious to place a C₁₋₄ alkyl group on the amino group in the two compounds depicted above, at the R³ position of those compounds. This modification is expressly suggested in the Cox et al publication.

Art Unit: 1624

The motivation to do so would have been to make anticonvulsant compounds for the treatment of epilepsy. Since Cox et al suggests that the R³ position can be alkylamino, in addition to the exemplified amino, one of ordinary skill would have a high expectation of success in obtaining a compound with anticonvulsant activity.

Specification

The abstract of the disclosure is objected to because it does not accurately describe the invention. When the invention is a group of chemical compounds, at least some generic structure of those compounds should be set out in the abstract of a patent wherein such an invention is disclosed. Currently, the abstract states that "5-substituted-2-aryl pyrazine compounds," are disclosed, which is no more descriptive of the compounds than the title of the application is. Since the abstract appears on the face of a printed patent, abstracts wherein a generic structure appears provide ease in searching patent literature to those who do so, whether they be patent examiners, attorneys or the general public. It is suggested that applicants place a generic structure diagram in the abstract.

Correction is required. See MPEP § 608.01(b).

Allowable Subject Matter

No compounds specified in claim 26 is disclosed in Yoon et al, and none in that claim are deemed obvious over Yoon et al. Most of the compounds in instant claim 26 are those wherein the 2-aryl ring is a pyridine ring. No such compounds are taught in Yoon et al. All compounds from claim 26 are allowable. That claim is an independent claim, so it is allowed. The only compound named in claim 11 found to be obvious in

Art Unit: 1624

light of Yoon et al is the one named above in the rejection of claim 11 under 35 U.S.C. 103(a). Deletion of that compound, N-(1-ethylpropyl)-3,6-dimethoxy-5-[2-methoxy-4 (trifluoromethoxy)-phenyl]pyrazin-2-amine, from claim 11 (page 16, second compound named on the page) would place that claim in allowable form.

Claims 3 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Yoon et al does not teach any "Ar" group other than phenyl. Claim 3 specifies that J is nitrogen, and so is novel and unobvious over Yoon et al.

Should conditions for rejoinder of Group II be met, which conditions are explained above in the section headed "Election/Restrictions" and those claims are rejoined, rejection thereof under 35 U.S.C. 112, first and second paragraphs, may be necessary. The term "stress," generally and without some sort of context, is not a distinct and clear medical term, rather the distinction between the presence and absence of stress, or between different kinds of stress is blurred, and treatment of all of the different types of stress within the broadest reasonable interpretation of the term does not appear to be enabled by the disclosure in light of the state of the art in CRF antagonist agents at the time the invention was made. It does not seem that treatment of Crohn's disease or irritable bowel syndrome with a CRF receptor antagonist was within the level of ordinary skill in 2002 either.

Two references which will provide an assessment of the state of the art and level of skill in the field of CRF receptor antagonists at the time the invention was made are:

Art Unit: 1624

Dautzenberg and Hauger, "The CRF peptide family and their receptors: yet more partners discovered" Trends in Pharmacological Sciences, vol. 23(2), pages 71-77 (February 2002).

and

Kehne and De Lombaert, "Non-Peptidic CRF₁ Receptor Antagonists for the Treatment of Anxiety, Depression and Stress Disorders" Current Drug Targets – CNS & Neurological Disorders, vol. 1(5), pages 467-493 (2002).

Conclusion

Any inquiry concerning this communication should be directed to Zachary Tucker whose telephone number is (571) 272-0677. The examiner can normally be reached Tuesday-Thursday from 8:00am to 4:30pm or Monday from 6:00am to 1:30pm. If Attempts to reach the examiner are unsuccessful, contact the examiner's supervisor, James O. Wilson, at (571) 272-0661.

The fax number for the organization where this application or proceeding is assigned is (571) 273-8300.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (571) 272-1600.

zt

A handwritten signature in black ink, appearing to be 'Z. Tucker' or similar, written in a cursive style.